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[54] **PHENYL HETEROCYCLES AS COX-2 INHIBITORS**

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[63] Continuation-in-part of Ser. No. 82,196, Jun. 24, 1993, abandoned.

[51] **Int. Cl.**[6] **A61K 31/53**; C07D 307/02

[52] **U.S. Cl.** **514/241**; 514/242; 514/252; 514/267; 514/359; 514/362; 514/363; 514/365; 514/372; 514/374; 514/378; 514/383; 514/451; 514/444; 514/473; 514/99; 514/461; 549/60; 549/295; 549/323; 549/218; 549/222; 544/180; 544/238; 544/333; 544/374; 548/127; 548/128; 548/131; 548/134; 548/136; 548/125; 548/143; 548/202; 548/206; 548/235; 548/247; 548/365.7; 548/255; 548/262.5

[58] **Field of Search** 549/218, 222, 549/295, 60, 323; 514/99, 451, 461, 241, 242, 252, 267, 359, 374, 378, 383, 444; 544/180, 238, 333, 374; 548/127, 128, 131, 134, 125, 136, 143, 202, 206, 235, 247, 365.7, 255, 262.5

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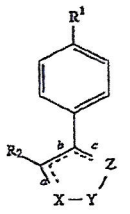
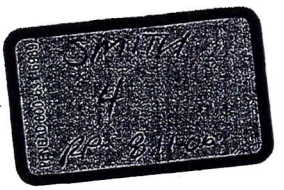
[57] **ABSTRACT**

The invention encompasses the novel compound of Formula I useful in the treatment of cyclooxygenase-2 mediated diseases,



The invention also encompasses certain pharmaceutical compositions for treatment of cyclooxygenase-2 mediated diseases comprising compounds of Formula I.

25 Claims, No Drawings



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PHENYL HETEROCYCLES AS COX-2 INHIBITORS

This application is a continuation-in-part of U.S. Ser. No. 08/082,196, filed Jun. 24, 1993 (abandoned).

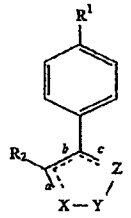
BACKGROUND OF THE INVENTION

This invention relates to compounds and pharmaceutical compositions for the treatment of cyclooxygenase mediated diseases and methods of treatment thereof.

Non-steroidal, antiinflammatory drugs exert most of their antiinflammatory, analgesic and antipyretic activity and inhibit hormone-induced uterine contractions and certain types of cancer growth through inhibition of prostaglandin G/H synthase, also known as cyclooxygenase. Up until recently, only one form of cyclooxygenase had been characterized. This corresponding to cyclooxygenase-1 or the constitutive enzyme, as originally identified in bovine seminal vesicles. Recently the gene for a second inducible form of cyclooxygenase (cyclooxygenase-2) has been cloned, sequenced and characterized from chicken, murine and human sources. This enzyme is distinct from the cyclooxygenase-1 which has now also been cloned, sequenced and characterized from sheep, munne and human sources. The second form of cyclooxygenase, cyclooxygenase-2, is rapidly and readily inducible by a number of agents including mitogens, endotoxin, hormones, cytokines and growth factors. As prostaglandins have both physiological and pathological roles, we have concluded that the constitutive enzyme, cyclooxygenase-1, is responsible, in large part, for endogenous basal release of prostaglandins and hence is important in their physiological functions such as the maintenance of gastrointestinal integrity and renal blood flow. In contrast, we have concluded that the inducible form, cyclooxygenase-2, is mainly responsible for the pathological effects of prostaglandins where rapid induction of the enzyme would occur in response to such agents as inflammatory agents, hormones, growth factors, and cytokines. Thus, a selective inhibitor of cyclooxygenase-2 will have similar antiinflammatory, antipyretic and analgesic properties to a conventional non-steroidal antiinflammatory drug, and in addition would inhibit hormone-induced uterine contractions mad have potential anti-cancer effects, but will have a diminished ability to induce some of the mechanism-based side effects. In particular, such a compound should have a reduced potential for gastrointestinal toxicity, a reduced potential for renal side effects, a reduced effect on bleeding times and possibly a lessened ability to induce asthma attacks in aspirin-sensitive asthmatic subjects.

SUMMARY OF THE INVENTION

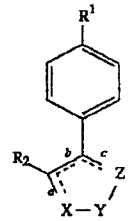
The invention encompasses novel compounds of Formula I useful in the treatment of cyclooxygenase-2 mediated diseases.



The invention also encompasses certain pharmaceutical compositions and methods for treatment of cyclooxygenase-2 mediated diseases comprising the use of compounds of Formula I.

DETAILED DESCRIPTION OF THE INVENTION

The invention encompasses the novel compound of Formula I useful in the treatment of cyclooxygenase-2 mediated diseases



I

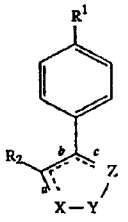
or pharmaceutically acceptable salts thereof wherein:
X-Y-Z-is selected from the group consisting of:

(a) —$CH_2CH_2CH_2$—,
(b) —$C(O)CH_2CH_2$—,
(c) —$CH_2CH_2C(O)$—,
(d) —$CR^5(R^5)$—O—C(O)—,
(e) —C(O)—O—$CR^5(R^{5'})$—,
(f) —CH_2—NR^3—CH_2—,
(g) —$CR^5(R^{5'})$—NR^3—C(O)—,
(h) —CR^4=$CR^{4'}$—S—,
(i) —S—CR^4=$CR^{4'}$—,
(j) —S—N=CH—,
(k) —CH=N—S—,
(l) —N=CR^4—O—,
(m) —O—CR4=N—,
(n) —N=CR^4—NH—;
(o) —N=CR^4—S—, and
(p) —S—CR^4—N—;
(q) —C(O)—NR^3—$CR^5(R^{5'})$—;
(r) —R^3N—CH=CH— provided R^1 is not —$S(O)_2$Me
(s) —CH=CH—NR^3— provided R^1 is not —$S(O)_2$Me

when side b is a double bond, and sides a an c are single bonds; and

X-Y-Z-is selected from the group consisting of:
(a) =CH—O—CH=, and
(b) =CH—NR^3—CH=,
(c) =N—S—CH=,
(d) =CH—S—N=,
(e) =N—O—CH=,
(f) =CH—O—N=,
(g) =N—S—N=,
(h) =N—O—N=,
when sides a and c are double bonds and side b is a single bond;
R^1 is selected from the group consisting of
(a) $S(O)_2CH_3$,
(b) $S(O)_2NH_2$,
(c) $S(O)_2NHC(O)CF_3$,
(d) $S(O)(NH)CH_3$,
(e) $S(O)(NH)NH_2$,
(f) $S(O)(NH)NHC(O)CF_3$,
(g) $P(O)(CH_3)OH$, and
(h) $P(O)(CH_3)NH_2$,
R^2 is selected from the group consisting of
(a) C_{1-6}alkyl,
(b) C_3, C_4, C_5, C_6, and C_7, cycloalkyl,
(c) mono-, di- or tri-substituted phenyl or naphthyl wherein the substituent is selected from the group consisting of
(1) hydrogen,
(2) halo,
(3) C_{1-6}alkoxy,
(4) C_{1-6}alkylthio,
(5) CN,
(6) CF_3,
(7) C_{1-6}alkyl,
(8) N_3,
(9) —CO_2H,
(10) —CO_2—C_{1-4}alkyl,
(11) —C(R^5)(R^6)—OH,
(12) —C(R^5)(R^6)—O—C_{1-4}alkyl, and
(13) —C_{1-6}alkyl—CO_2—R^5;
(d) mono-, di- or tri-substituted heteroaryl wherein the heteroaryl is a monocyclic aromatic ting of 5 atoms, said ting having one hetero atom which is S, O, or N, and optionally 1, 2, or 3 additionally N atoms; or the heteroaryl is a monocyclic ting of 6 atoms, said ring having one hetcro atom which is N, and optionally 1, 2, 3, or 4 additional N atoms; said substituents are selected from the group consisting of
(1) hydrogen,
(2) halo, including fluoro, chloro, bromo and iodo,
(3) C_{1-6}alkyl,
(4) C_{1-6}alkoxy,
(5) C_{1-6}alkylthio,
(6) CN,
(7) CF_3,
(8) N_3,
(9) —C(R^5)(R^6)—OH, and
(10) —C(R^5)(R^6)—O—C_{1-4}alkyl;
(e) benzoheteroaryl which includes the benzo fused analogs of (d) ;
R^3 is selected from the group consisting of
(a) hydrogen,
(b) CF_3,
(c) CN,
(d) C_{1-6}alkyl,
(c) hydroxy C_{1-6}alkyl,
(f) —C(O)—C_{1-6}alkyl,
(g) optionally substituted
(1) —C_{1-5}alkyl—Q,
(2) —C_{1-3}alkyl—O—C_{1-3}alkyl—Q,
(3) —C_{1-3}alkyl—S—C_{1-3}alkyl—Q,
(4) —C_{1-5}alkyl—O—Q, or
(5) —C_{1-5}alkyl—S—Q,
wherein the substituent resides on the alkyl and the substituent is C_{1-3}alkyl;
(h) —Q
R^4 and R$^{4'}$ are each independently selected from the group consisting of
(a) hydrogen,
(b) CF_3,
(c) CN,
(d) C_{1-6}alkyl,
(e) —Q,
(f) —O—Q;
(g) —S—Q, and
(h) optionally substituted
(1) —C_{1-5}alkyl—Q,
(2) —O—C_{1-5}alkyl—Q,
(3) —S—C_{1-5}alkyl—Q,
(4) —C_{1-3}alkyl—O—C_{1-3}alkyl—Q,
(5) —C_{1-3}alkyl—S—C_{1-3}alkyl—Q,
(6) —C_{1-5}alkyl—O—Q,
(7) —C_{1-5} alkyl—S—Q,
wherein the substituent resides on the alkyl and the substituent is C_{1-3}alkyl, and
R^5, R$^{5'}$, R^6, R^7 and R^8 are each independently selected from the group consisting of
(a) hydrogen,
(b) C_{1-6}alkyl,
or R^5 and R^6 or R^7 and R^8 together with the carbon to which they are attached form a saturated monocyclic carbon ring of 3, 4, 5, 6 or 7 atoms;
Q is CO_2H, CO_2—C_{1-4}alkyl, tetrazolyl-5-yl, C(R^7)(R^8)(OH), or C(R^7)(R^8)(O—C_{1-4}alkyl);
provided that when X-Y-Z is —S—CR^4=CR$^{4'}$, then R^4 and R$^{4'}$ are other than CF_3.

One Class within this embodiment are the compounds of formula I



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or pharmaceutically acceptable salts thereof wherein:
X-Y-Z- is selected from the group consisting of —C(O)—O—CR^5(R$^{5'}$)— when side b is a double bond, and sides a and c are single bonds; and
R^1 is selected from the group consisting of
(a) $S(O)_2CH_3$,
(b) $S(O)_2NH_2$,
R^2 is selected from the group consisting of
(a) C_{1-6}alkyl,

(b) C_3, C_4, C_5, C_6, and C_7 cycloalkyl,

(c) heteroaryl

(d) benzoheteroaryl

(e) mono- or di-substituted phenyl wherein the substituent is selected from the group consisting of

(1) hydrogen,

(2) halo,

(3) C_{1-6}alkoxy,

(4) C_{1-6}alkylthio,

(5) CN,

(6) CF_3,

(7) C_{1-6}alkyl,

(8) N_3,

(9) $—CO_2H$,

(10) $—CO_2—C_{1-4}$alkyl,

(11) $—C(R^5)(R^6)—OH$,

(12) $—C(R^5)(R^6)—O—C_{1-4}$alkyl, and

(13) $—C_{1-6}$alkyl$—CO_2—R^5$;

R^5, R^{5a} and R^6 are each independently selected from the group consisting of

(a) hydrogen,

(b) C_{1-6}alkyl,

or R^5 and R^6 together with the carbon to which they are attached form a saturated monocyclic carbon ring of 3, 4, 5, 6 or 7 atoms.

For purposes of this specification alkyl is defined to include linear, branched, and cyclic structures, with C_{1-6}alkyl including including methyl, ethyl, propyl, 2-propyl, s- and t-butyl, butyl, pentyl, hexyl, 1,1-dimethylethyl, cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl. Similarly, C_{1-6}alkoxy is intended to include alkoxy groups of from 1 to 6 carbon atoms of a straight, branched, or cyclic configuration. Examples of lower alkoxy groups include methoxy, ethoxy, propoxy, isopropoxy, cyclopropyloxy, cyclohexyloxy, and the like. Likewise, C_{1-6}alkylthio is intended to include alkylthio groups of from 1 to 6 carbon atoms of a straight, branched or cyclic configuration. Examples of lower alkylthio groups include methylthio, propylthio, isopropylthio, cycloheptylthio, etc. By way of illustration, the propylthio group signifies $—SCH_2CH_2CH_3$.

Heteroaryl includes furan, thiophene, pyrrole, isoxazole, isothiazole, pyrazole, oxazole, thiazole, imidazole, 1,2,3-oxadiazole, 1,2,3-thiadiazole, 1,2,3-triazole, 1,3,4-oxadiazole, 1,3,4-thiadiazole, 1,3,4-triazole, 1,2,5-oxadiazole, 1,2,5-thiadiazole, pyridine, pyridazine, pyrimidine, pyrazine, 1,2,4-triazine, 1,3,5-triazine, 1,2,4,5-tetrazine, and the like.

Benzoheteroaryl includes the above heteroaryl rings to which it is possible to fuse a benzene ring.

Exemplifying the invention are:

(a) 3-(4-(Aminosulfonyl)phenyl)-2-(4-fluorophenyl)-5-(2-hydroxy-2-propyl)thiophene,

(b) 3-(4-(Aminosulfonyl)phenyl)-2-(4-fluorophenyl)thiophene,

(c) 3-(4-(Aminosulfonyl)phenyl)-2-(4-fluorophenyl)-5-(2-propyl)thiophene,

(d) 3-(4-(Aminosulfonyl)phenyl)-2-cyclohexylthiophene,

(e) 5-(4-Carboxyphenyl)-4-(4-(methylsulfonyl)phenyl)thiophene-2-carboxylic acid,

(f) 4-(4-Fluorophenyl)-2-methyl-5-(4-(methylsulfonyl)phenyl)thiazole,

(g) 2-(4-Fluorophenyl)-3-(4-(methylsulfonyl)phenyl)-2-cyclopenten-1-one

(h) 4-(4-(Methylsulfonyl)phenyl)-5-(4-fluorophenyl-)isothiazole,

(i) 3-(4-Fluorophenyl)-4-(4-(methylsulfonyl)phenyl)-2-(5H)-furanone,

(j) 3-(4-Fluorophenyl)-4-(4-(aminosulfonyl)phenyl)-2-(5H)-furanone,

(k) 3-(4-Fluorophenyl)-4-(4-(methylsulfonyl)phenyl)furan,

(l) 5,5-Dimethyl-3-(4-fluorophenyl)-4-(4-methylsulfonyl)phenyl)-2-(5H)-furanone,

(m) 2-(4-(Aminosulfonyl)phenyl)-3-(4-fluorophenyl)thiophene, and

(n) 3-(4-(Trifluoroacetylaminosulfonyl)phenyl)-2-(4-fluorophenyl)thiophene,

(o) 3-(3-Fluorophenyl)-4-(4-(methylsulfonyl)phenyl)-2-(5H)-furanone,

(p) 5,5-Dimethyl-3-(3-fluorophenyl)-4-(4-methylsulfonyl)phenyl)-2-(5H)-furanone,

(q) 5,5-Dimethyl-3-(3-chlorophenyl)-4-(4-methylsulfonyl)phenyl)-2-(5H)-furanone,

(r) 3-(3,4-Difluorophenyl)-4-(4-(methylsulfonyl)phenyl)-2-(5H)-furanone,

(s) 3-(3,4-Dichlorophenyl)-4-(4-(methylsulfonyl)phenyl)-2-(5H)-furanone,

(t) 5,5-Dimethyl-3-(3,4-difluorophenyl)-4-(4-methylsulfonyl)phenyl)-2-(5H)-furanone,

(u) 5,5-Dimethyl-3-(3,4-dichlorophenyl)-4-(4-methylsulfonyl)phenyl)-2-(5H)-furanone,

(v) 5,5-Dimethyl-3-(4-chlorophenyl)-4-(4-methylsulfonyl)phenyl)-2-(5H)-furanone,

(w) 3-(2-Naphyhyl)-4-(4-(methylsulfonyl)phenyl)-2-(5H)-furanone,

(x) 5,5-Dimethyl-3-(2-naphyhyl)-4-(4-(methylsulfonyl)phenyl)-2-(5H)-furanone,

(y) 3-phenyl-4-(4-(methylsulfonyl)phenyl)-2-(5H)-furanone.

Some of the compounds described herein contain one or more asymmetric centers and may thus give rise to diastereomers and optical isomers. The present invention is meant to comprehend such possible diastereomers as well as their racemic and resolved, enantiomerically pure forms and pharmaceutically acceptable salts thereof.

Some of the compounds described herein contain olefinic double bonds, and unless specified otherwise, are meant to include both E and Z geometric isomers.

In a second embodiment, the invention encompasses pharmaceutical compositions for inhibiting cyclooxygenase and for treating cyclooxygenase mediated diseases as disclosed herein comprising a pharmaceutically acceptable carder and a non-toxic therapeutically effective amount of compound of formula I as described above.

Within this embodiment the invention encompasses pharmaceutical compositions for inhibiting cyclooxygenase-2 and for treating cyclooxygenase-2 mediated diseases as disclosed herein comprising a pharmaceutically acceptable carder and a non-toxic therapeutically effective amount of compound of formula I as described above.

In a third embodiment, the invention encompasses a method of inhibiting cyclooxygenase and treating cyclooxygenase mediated diseases, advantageously treated by an active agent that selectively inhibits COX-2 in preference to COX-1 as disclosed herein comprising: administration to a patient in need of such treatment of a non-toxic therapeutically effective amount of a compound of Formula I as disclosed herein.

For purposes of this specification a compound is said to selectively inhibit COX-2 in preference to COX-1 if the ratio of the IC50 concentration for COX-1 inhibition to

COX-2 inhibition is 100 or greater.

The pharmaceutical compositions of the present invention comprise a compound of Formula I as an active ingredient or a pharmaceutically acceptable salt, thereof, and may also contain a pharmaceutically acceptable carrier and optionally other therapeutic ingredients. The term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic bases including inorganic bases and organic bases. Salts derived from inorganic bases include aluminum, ammonium, calcium, copper, ferric, ferrous, lithium, magnesium, manganic salts, manganous, potassium, sodium, zinc, and the like. Particularly preferred are the ammonium, calcium, magnesium, potassium, and sodium salts. Salts derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines, and basic ion exchange resins, such as arginine, betaine, caffeine, choline, N,N-dibenzylethylenediamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethylmorpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine, tripropylamine, tromethamine, and the like.

It will be understood that in the discussion of methods of treatment which follows, references to the compounds of Formula I are meant to also include the pharmaceutically acceptable salts.

The Compound of Formula I is useful for the relief of pain, fever and inflammation of a variety of conditions including rheumatic fever, symptoms associated with influenza or other viral infections, common cold, low back and neck pain, dysmenorrhea, headache, toothache, sprains and strains, myositis, neuralgia, synovitis, arthritis, including rheumatoid arthritis degenerative joint diseases (osteoarthritis), gout and ankylosing spondylitis, bursitis, burns, injuries, following surgical and dental procedures. In addition, such a compound may inhibit cellular neoplastic transformations and metastic tumor growth and hence can be used in the treatment of cancer. Compounds of formula I may also be useful for the treatment of dementia including pre-senile and senile dementia, and in particular, dementia associated with Alzheimer Disease (ie Alzheimer's dementia).

Compounds of formula I will also inhibit prostanoid-induced smooth muscle contraction by preventing the synthesis of contractile prostanoids and hence may be of use in the treatment of dysmenorrhea, premature labor and asthma.

By virtue of its high cyclooxygenase-2 (COX-2) activity and/or its selectivity for cyclooxygenase-2 over cyclooxygenase-1 (COX-1) as defined above, compounds of formula I will prove useful as an alternative to conventional non-steroidal antiinflanunatory drugs (NSAID'S) particularly where such non-steroidal antiinflammatory drugs may be contra-indicated such as in patients with peptic ulcers, gastritis, regional enteritis, ulcerative colitis, diverticulitis or with a recurrent history of gastrointestinal lesions; GI bleeding, coagulation disorders including anemia such as hypoprothrombinemia, haemophilia or other bleeding problems (including those relating to reduced or impaired platelet function); kidney disease (eg impaired renal function); those prior to surgery or taking anticoagulants; and those susceptable to NSAID induced asthma.

Similarly, compounds of formula I, will be useful as a partial or complete substitute for conventional NSAID'S in preparations wherein they are presently co-administered with other agents or ingredients. Thus in further aspects, the invention encompasses pharmaceutical compositions for treating cyclooxygenase-2 mediated diseases as defined above comprising a non-toxic therapeutically effective amount of the compound of Formula I as defined above and one or more ingredients such as another pain reliever including acetominophen or phenacetin; a potentiator including caffeine; an H2-antagonist, aluminum or magnesium hydroxide, simethicone, a decongestant including phenylephrine, phenylpropanolamine, pseudophedrine, oxymetazoline, ephinephrine, naphazoline, xylometazoline, propylhexedrine, or levo-desoxyephedrine; an antiitussive including codeine, hydrocodone, caramiphen, carbetapentane, or dextramethorphan; a diuretic; a sedating or non-sedating antihistamine. In addition the invention encompasses a method of treating cyclooxygenase mediated diseases comprising: administration to a patient in need of such treatment a non-toxic therapeutically effect amount of the compound of Formula I, optionally co-administered with one or more of such ingredients as listed immediately above.

Compounds of the present invention are inhibitors of cyclooxygenase-2 and are thereby useful in the treatment of cyclooxygenase-2 mediated diseases as enumerated above. This activity is illustrated by their ability to selectively inhibit cyclooxygenase-2 over cyclooxygenase-1. Accordingly, in one assay, the ability of the compounds of this invention to treat cyclooxygenase mediated diseases can be demonstrated by measuring the amount of prostaglandin E_2 (PGE_2) synthesized in the presence of arachidonic acid, cyclooxygenase-1 or cyclooxygenase-2 and a compound of formula I. The IC50 values represent the concentration of inhibitor required to return PGE_2 synthesis to 50% of that obtained as compared to the uninhibited control. Illustrating this aspect, we have found that the Compounds of the Examples are more than 100 times more effective in inhibiting COX-2 than they are at inhibiting COX-1. In addition they all have a COX-2 IC50 of 1 nM to 1 μM. By way of comparison, Ibuprofen has an IC50 for COX-2 of 1 μM, and Indomethacin has an IC50 for COX-2 of approximately 100 nM. For the treatment of any of these cyclooxygenase mediated diseases, compounds of formula I may be administered orally, topically, parenterally, by inhalation spray or rectally in dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carders, adjuvants and vehicles. The term parenteral as used herein includes subcutaneous injections, intravenous, intramuscular, intrastemal injection or infusion techniques. In addition to the treatment of warm-blooded animals such as mice, rats, horses, cattle sheep, dogs, cats, etc., the compound of the invention is effective in the treatment of humans.

As indicated above, pharmaceutical compositions for treating cyclooxygenase-2 mediated diseases as defined may optionally include one or more ingredients as listed above.

The pharmaceutical compositions containing the active ingredient may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, or syrups or elixirs. Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture

of tablets. These excipients may be for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; binding agents, for example starch, gelatin or acacia, and lubricating agents, for example, magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed. They may also be coated by the technique described in the U.S. Pat. Nos. 4,256,108; 4,166,452; and 4,265,874 to form osmotic therapeutic tablets for control release.

Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredients is mixed with water or an oil medium, for example peanut oil, liquid paraffin, or olive oil.

Aqueous suspensions contain the active material in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydroxy-propylmethycellulose, sodium alginate, polyvinyl-pyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally-occurring phosphatide, for example lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethylene-oxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives, for example ethyl, or n-propyl, p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, and one or more sweetening agents, such as sucrose, saccharin or aspartame.

Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set forth above, and flavoring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example sweetening, flavoring and coloring agents, may also be present.

The pharmaceutical compositions of the invention may also be in the form of an oil-in-water emulsions. The oily phase may be a vegetable oil, for example olive oil or arachis oil, or a mineral oil, for example liquid paraffin or mixtures of these. Suitable emulsifying agents may be naturally-occurring phosphatides, for example soy bean, lecithin, and esters or partial esters derived from fatty acids and hexitol anhydrides, for example sorbitan monooleate, and condensation products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening and flavouring agents.

Syrups and elixirs may be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative and flavoring and coloring agents. The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleagenous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example as a solution in 1,3-butane diol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

Compounds of formula I may also be administered in the form of a suppositories for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials are cocoa butter and polyethylene glycols.

For topical use, creams, ointments, jellies, solutions or suspensions, etc., containing the compound of Formula I are employed. (For purposes of this application, topical application shall include mouth washes and gargles.)

Dosage levels of the order of from about 0.01 mg to about 140 mg/kg of body weight per day are useful in the treatment of the above-indicated conditions, or alternatively about 0.5 mg to about 7 g per patient per day. For example, inflammation-may be effectively treated by the administration of from about 0.01 to 50 mg of the compound per kilogram of body weight per day, or alternatively about 0.5 mg to about 3.5 g per patient per day.

The amount of active ingredient that may be combined with the carder materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. For example, a formulation intended for the oral administration of humans may contain from 0.5 mg to 5 g of active agent compounded with an appropriate and convenient amount of carder material which may vary from about 5 to about 95 percent of the total composition. Dosage unit forms will generally contain between from about 1 mg to about 500 mg of an active ingredient, typically 25 mg, 50 mg, 100 mg, 200 mg, 300 mg, 400 mg, 500 mg, 600 mg, 800 mg, or 1000 mg.

It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the age, body weight, general health, sex, diet, time of administration, route of administration, rate of excretion, drug combination and the severity of the particular disease undergoing therapy.

Methods of Synthesis

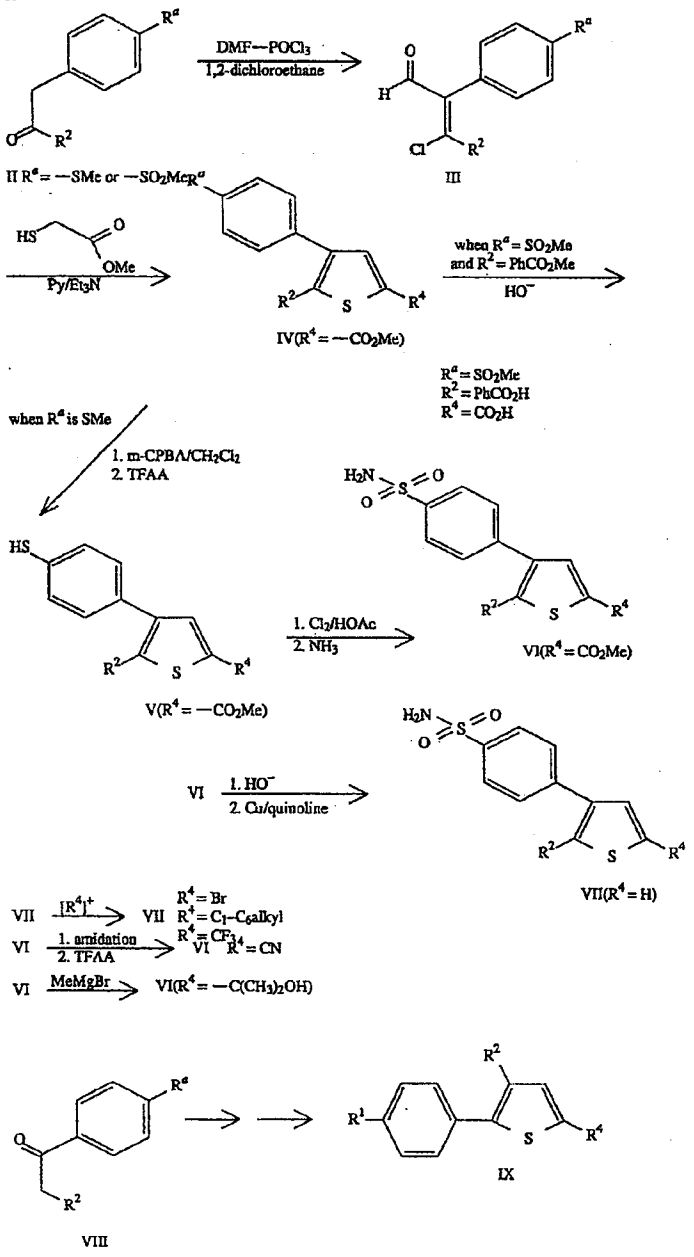
The compounds of the present invention can be prepared according to the following methods.

Method A:

The β-chlorovinylaldehyde III can be obtained from the ketone II and the Viismeier reagent (DMF-$POCl_3$) using the general method described by Weissenfels (Z. Chem. 1966, 6, 471). The thiophene compound IV is obtained from III using the general method described by Weissenfels (Z. Chem., 1973, 13, 57). The thiol compound V can be obtained after oxidation of compound IV (R^4=—SMe) with one equivalent of m-CPBA followed by treatment of the resulting sulfoxide with TFAA at reflux. The sulfonamide group (VI) can then be formed by the method of Kharash (J. Amer. Chem. Soc. 1951, 73, 3240). The hydrolysis of compound VI and decarboxylation with Cu bronze in quinoline provides compound VII. Compound VII (R^4=H) can be treated with halogenating agent such as bromine in acetic acid to allow the preparation of the 5-bromothiophene (VII, R^4=Br). When it is desired to have a nitrile group at C-5, this can be accomplished from VI via amide formation using the Weinreb methodology (Tetrahedron Letters, 1977, 4171) followed by dehydration with TFAA. The CF_3 group can be introduced at C-5 of VII via the method of Girard (J. Org. Chem. 1983, 48, 3220).

The introduction of an alkyl group at C-5 can be achieved via a Friedel-Crafts reaction on VII (R^4=H) and an acyl chloride, Cl-CO-lower alkyl and a catalyst such as $TiCl_4$, followed by reduction. For R^4=Me, this can be achieved from the ester (R^4=CO_2Me) via a DIBAL-H reduction followed by deoxygenation using the method of Lau (J. Org. Chem. 1986, 51, 3038). Tertiary alcohols (R^4=—$C(CH_3)_2OH$) can be obtained from VI and MeMgBr. These tertiary alcohols can also be deoxygenated using the method of Lau. Similarly, the thiophene IX can be prepared from ketone VIII.

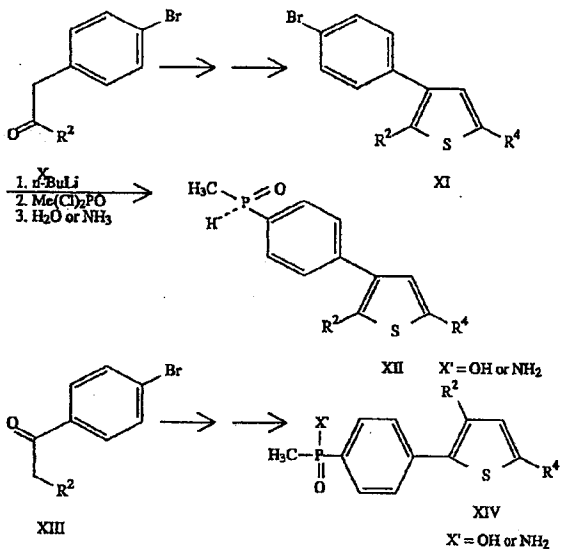
METHOD A



Method B

Ketone X can be converted to the thiophene compound XI using general methods already described in Method A. The thiophene XII can be prepared by metallation of XI with n-BuLi, quenching with methyl phosphonic dichloride and addition of water or ammonia (X'=OH or NH_2). Similarly, the other regioisomer XIV can be prepared from ketone XIII.

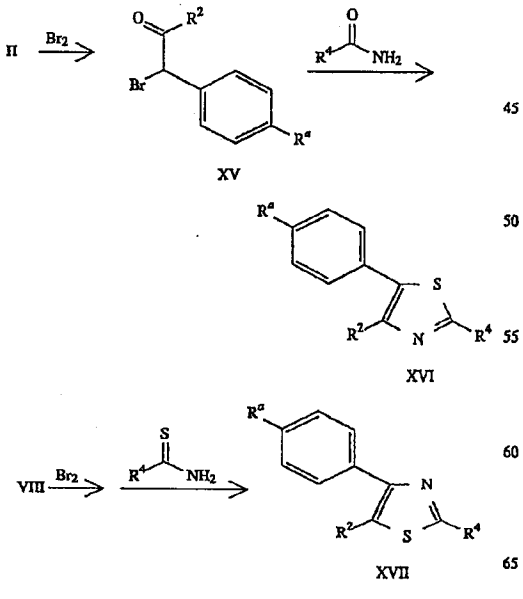
METHOD B



Method C

Bromination of ketone II gives the oc-bromoketone XV which is then convened to the thiazole XVI after treatment with a thioamide. Similarly, ketone VIII can be convened to thiazole XVII.

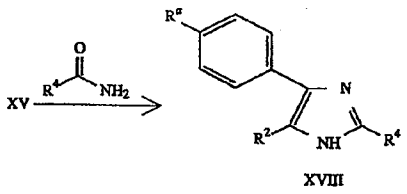
METHOD C



Method D

Ketone XV can be convened to the imidazole compound XVIII after treatment with formamide using the preparation of Brederick et al, Chem. Ber. 1953, p. 88.

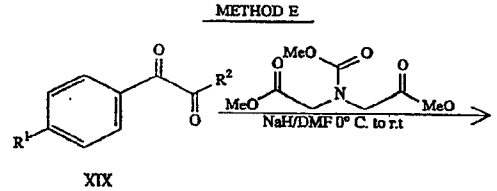
METHOD D



Method E

Pyrole compound XX can be obtained from dikctonc XIX using the general procedures of Friedman et al, J. Org. Chem. 1965, 30, p. 854, K. Dimroth et al, Ber. 1956, 56, 2602, K.Dimroth et al, Ann. 1961, 634, 102. The free NH of the pyrole can be acylated with Cl-CO-lower alkyl in the presence of a base such as Et_3N. Also alkylated products can be prepared using alkyl halides as reagents with a base such as NaH.

METHOD E



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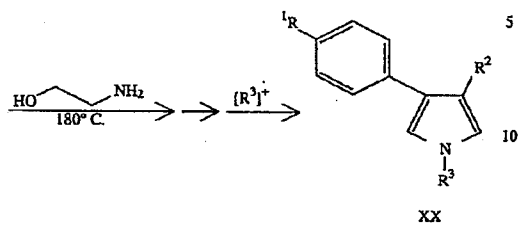
METHOD E

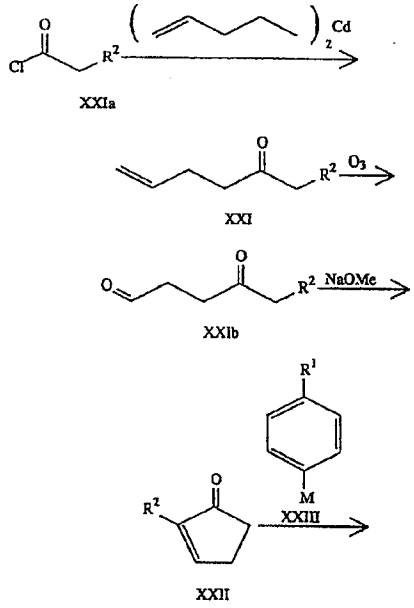


XX

Method F

The compounds of type XXV can be prepared from readily available 4-substituted phenylacetyl chlorides XXIa. Reaction of di(3-butenyl)cadmium with a 4-substituted phenylacetyl chloride provides ketone XXI. Ozonolysis of XXI affords keto aldehyde XXIb which is cyclized by base to give cyclopentenone XXII. Addition of arylmagnesium bromide or aryllithium to XXII gives allylic alcohol XXIV. Oxidation of XXIV with pyridinium chlorochromate affords the desired 2,3-disubstituted cyclopentenone XXV. For preparation of compound XXV (R^1=SO_2Me), 4-methylthiophenyllithium is used followed by oxidation with the magesium salt of monoperoxyphthalic acid (MMPP) or m-chloroperoxybenzoic acid (mCPBA) to introduce the required methylsulfonyl group in XXV.

METHOD F



XXIa XXI XXIb XXII

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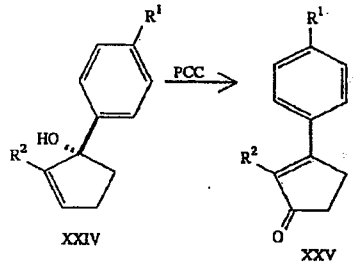
METHOD F

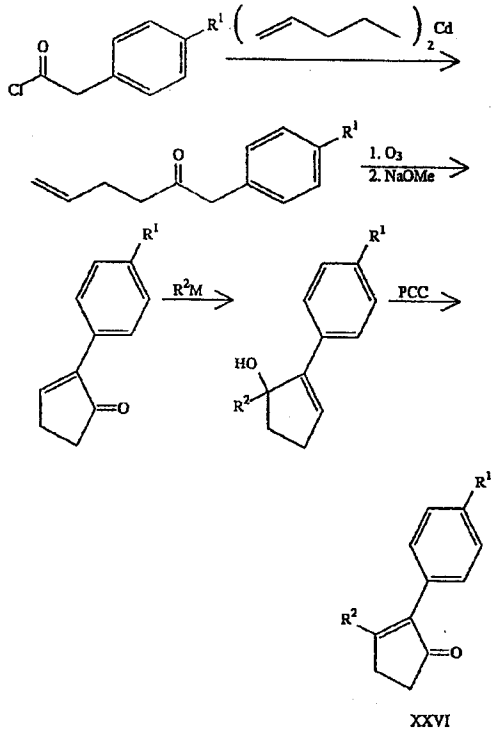


XXIV XXV

Method G

The sequence of Method G is the same as in Method F except R^1 containing acid chloride is used as starting material. R^2 is introduced at a later stage via a carbonyl addition reaction, followed by PCC oxidation.

METHOD G



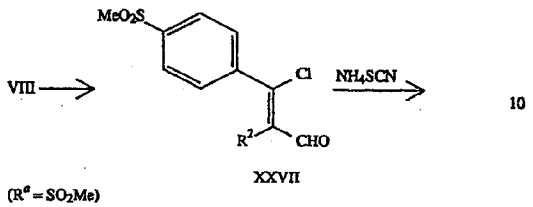
XXVI

Method H

The 4,5-disubstituted isothiazoles and isothiazol-3(2H)-one-1,1-dioxides can be prepared by the general method described by B. Schulze et al, Helvetica Chimica Acta, 1991,74, 1059. Thus, aldehyde III (R^a=SO_2Me) or XXVII is treated with excess NH_4SCN in refluxing acetone to provide the corresponding 4,5-disubstimted isothiazoles

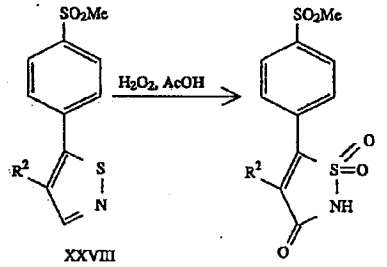
XXX and XXVIII, oxidation of which with hydrogen peroxide yields XXXI and XXIX.

METHOD H

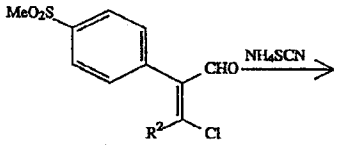


XXVII

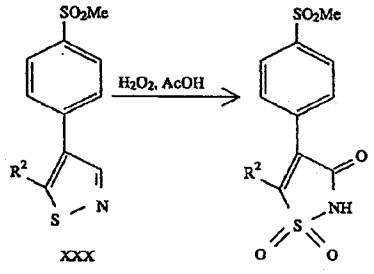
($R^a = SO_2Me$)



XXVIII XXIX



III($R_a = SO_2Me$)



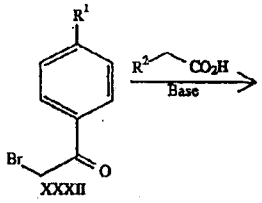
XXX XXXI

Method I

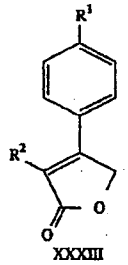
An appropriately substituted aryl bromomethyl ketone is reacted with an appropriately substituted aryl acetic acid in a solvent such as acetonitrile in the presence of a base such as triethylamine and then treated with 1,8-diazabicyclo [5.4.0]undec-7-ene (DBU) to afford either the lactone XXXIII or XXXV.

METHOD I

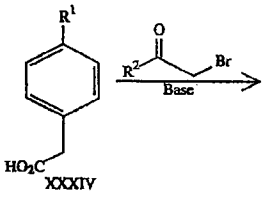
-continued



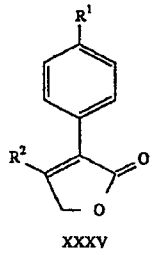
XXXII



XXXIII



XXXIV



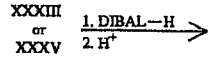
XXXV

(R^2 is a mono- or disubstituted phenyl or a mono- or disubstituted heteroaryl)

Method J

Either of the lactones XXXIII or XXXV in a solvent such as THF is reacted with a reducing agent such as diisobutyl aluminium hydride or lithium borohydride at −78° C., to yield the furan XXXVI.

METHOD J



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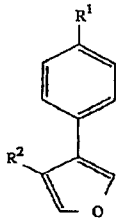
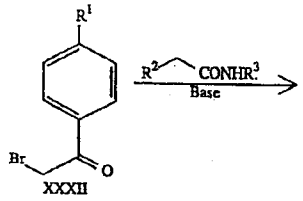


XXXVI

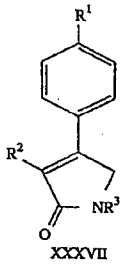
Method K

The preparation of lactams XXXVII and XXXIX can be achieved by the same reaction as described in Method I, except an appropriate amide is used.

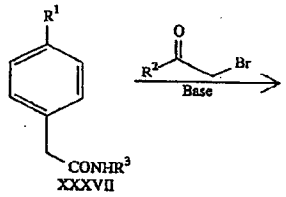
METHOD K



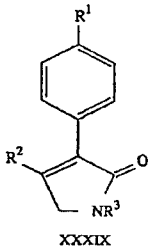
XXXII



XXXVII



XXXVII

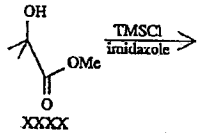


XXXIX

Method L

Methyl 2-hydroxy isobutyrate is silylated with TMSCl to give the TMS ether XXXXI, which is treated with 4-methylthiophenyllithium to provide ketone XXXXII. Desilylation followed by acylation yields ketoester XXXXIV, which can be cyclized to lactone XXXXV by base catalysis. Oxidation of XXXXV with MMPP or mCPBA affords the desired product XXXXVI.

METHOD L



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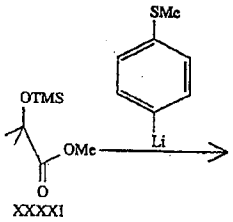
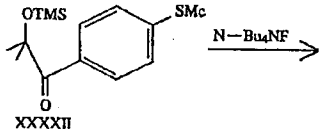
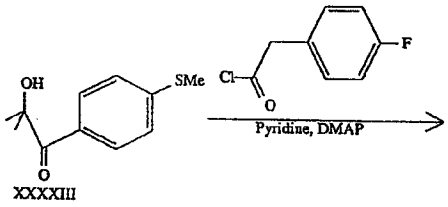


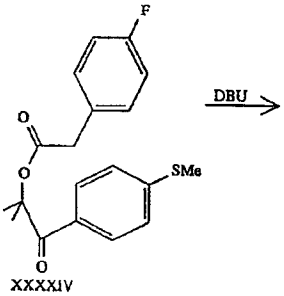
XXXXI



XXXXII

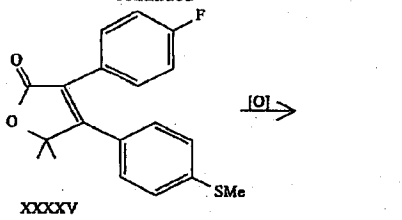


XXXXIII

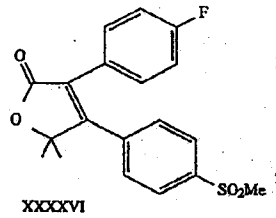


XXXXIV

-continued

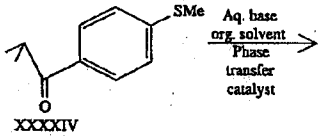


XXXXV

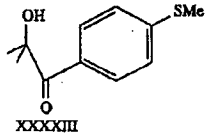


XXXXVI

METHOD M



XXXXIV



XXXXIII

An alternative preparation of the hydroxy ketone XXXXIII is the oxidation of the known (J. Org. Chem. 1991 56, 5955–8; Sulfur Lett. 1991, 12, 123–32) ketone XXXXIV. A mixture of XXXXIV, aquous base, such as NaOH, organic solvents such as carbon tetrachloride/toluene and a phase transfer catalyst such as ALIQUAT 336 is stirred in air at room temperature to provide XXXXIII. Compound XXXXIII is also described in U.S. Pat. No. 4,321,118 and Org. Coat. 1986, 6, 175–95.

Representative Compounds

Tables I and II illustrate compounds of formula I.

TABLE I

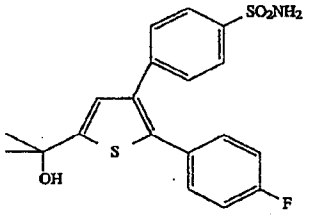
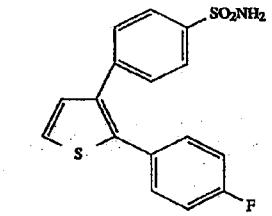
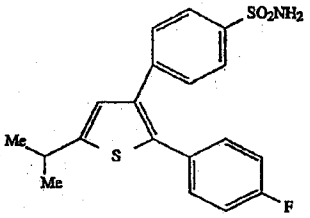
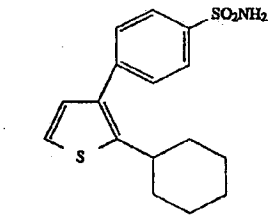
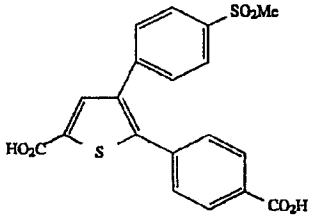
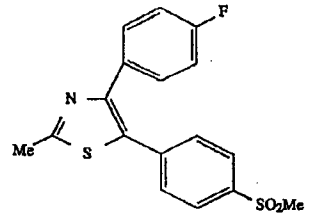
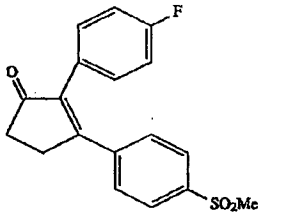
	Example	Method
	1	A
	2	A
	3	A
	4	A
	5	A
	6	C
	7	F

TABLE I-continued

TABLE I-continued

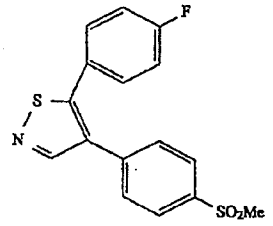
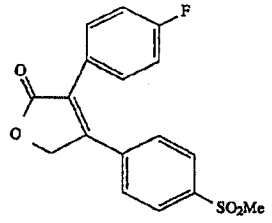
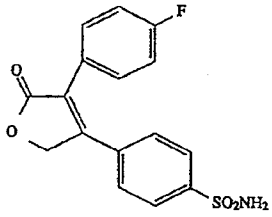
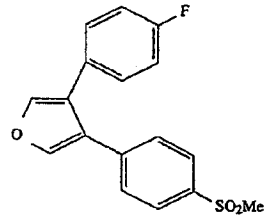
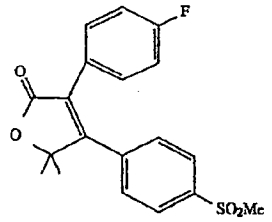
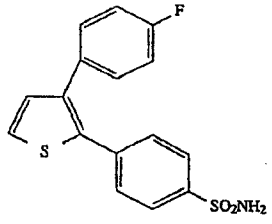
	Example	Method
	8	H
	9	I
	10	I
	11	J
	12	L
	13	A

TABLE I-continued

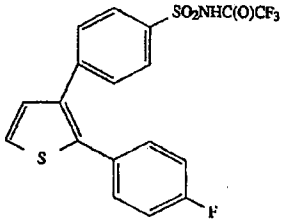
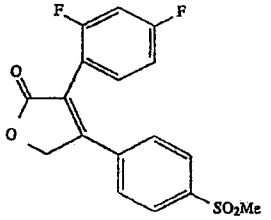
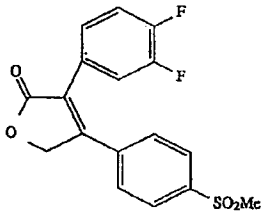
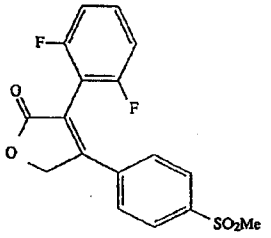
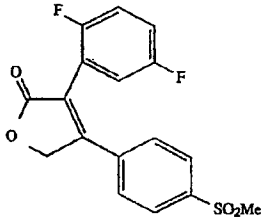
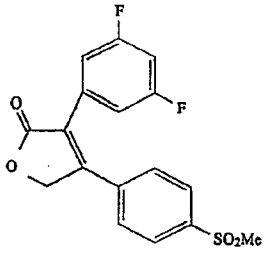
	Example	Method
	14	A
	15	I
	16	I
	17	I
	18	I
	19	I

TABLE I-continued

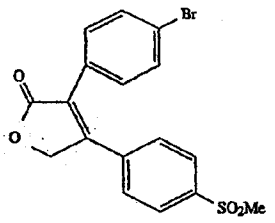
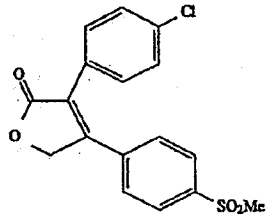
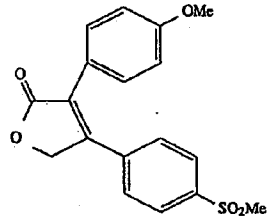
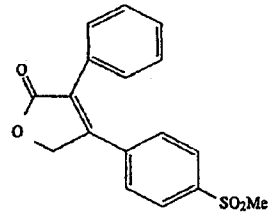
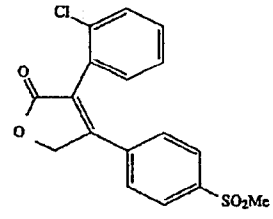
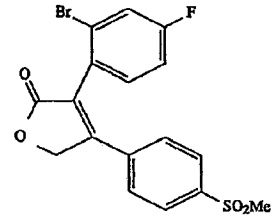
	Example	Method
	20	I
	21	I
	22	I
	23	I
	24	I
	25	I

TABLE I-continued

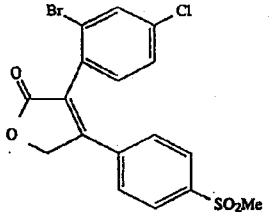
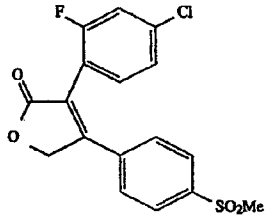
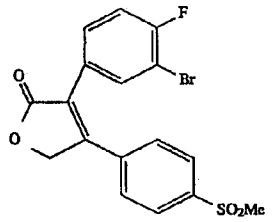
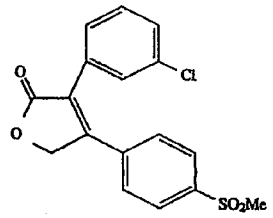
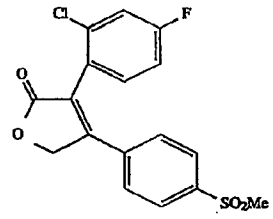
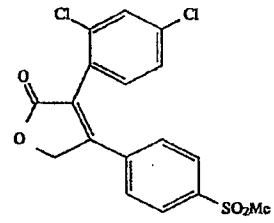
	Example	Method
	26	I
	27	I
	28	I
	29	I
	30	I
	31	I

TABLE I-continued

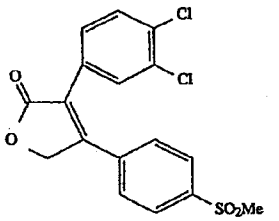
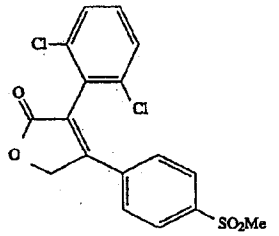
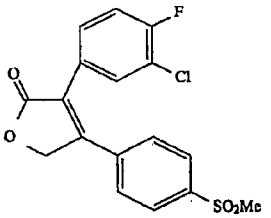
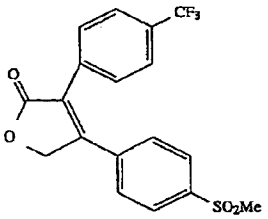
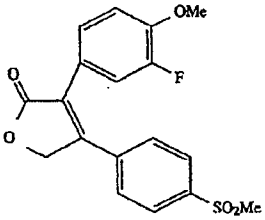
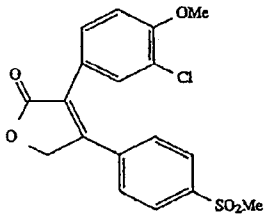
	Example	Method
	32	I
	33	I
	34	I
	35	I
	36	I
	37	I

TABLE I-continued

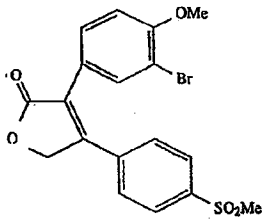
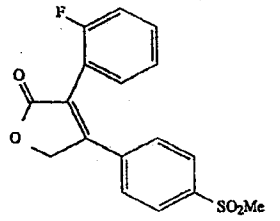
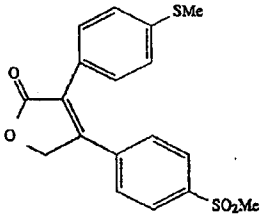
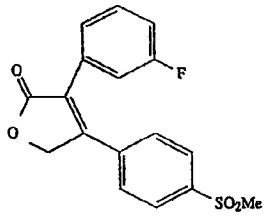
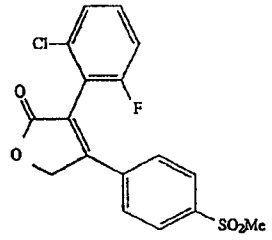
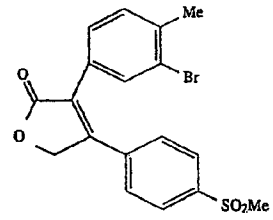
	Example	Method
	38	I
	39	I
	40	I
	41	I
	42	I
	43	I

TABLE I-continued

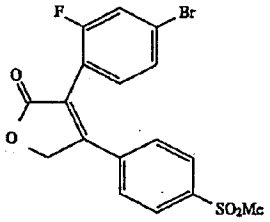
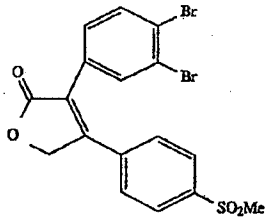
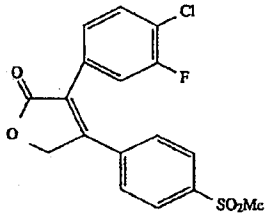
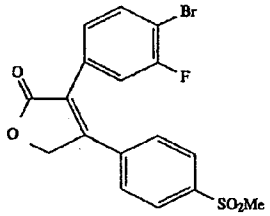
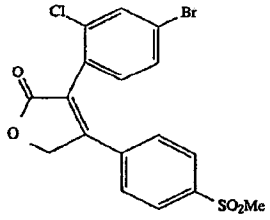
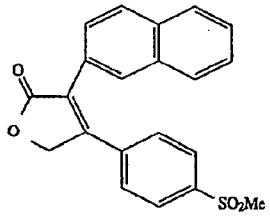
	Example	Method
	44	I
	45	I
	46	I
	47	I
	48	I
	49	I

TABLE I-continued

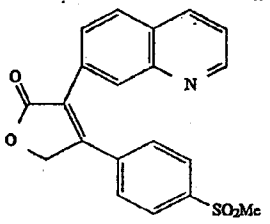
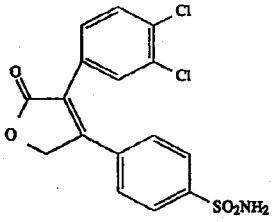
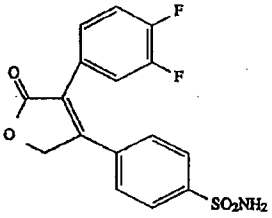
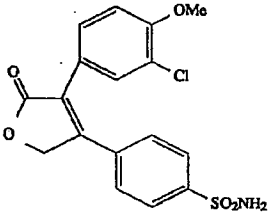
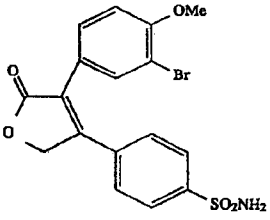
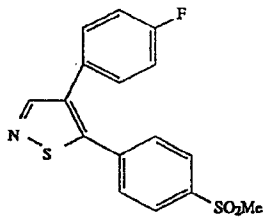
	Example	Method
	50	I
	51	I
	52	I
	53	I
	54	I
	55	H

TABLE I-continued

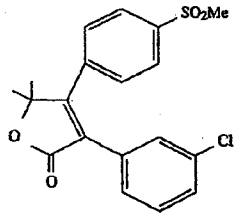
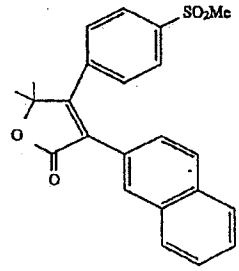
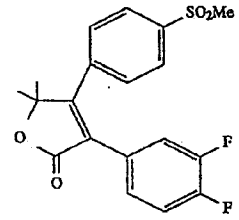
	Example	Method
	56	L + M
	57	L + M
	58	L + M

TABLE I-continued

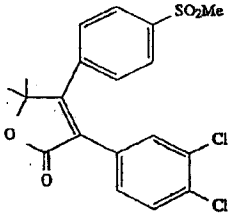
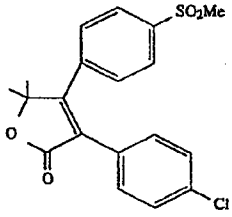
	Example	Method
	59	L + M
	60	L + M

TABLE II

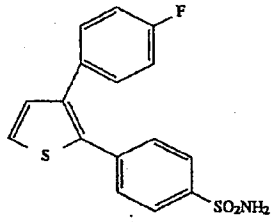
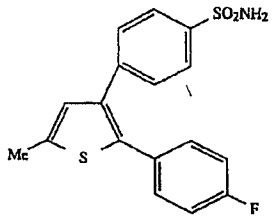
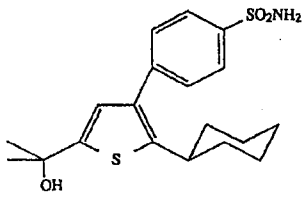
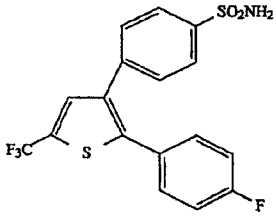
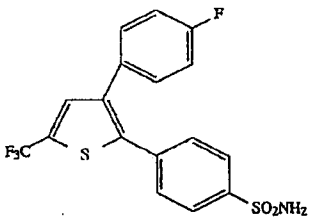
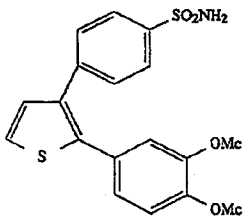







TABLE II-continued